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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/813,781	03/07/97	WEIDANZ J	45745

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EXAMINER	
LUBET, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/813,781	Applicant(s) Weidanz et al.
	Examiner Lubet	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Mar 5, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 6-9, 13-15, and 18-68* is/are pending in the application.

Of the above, claim(s) *3, 9, 13, 15, 21-60, 62-64, 66, and 68* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4, 6-8, 14, 18-20, 61, 65, and 67* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11,15*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This office action is in response to Paper 13 filed Jan. 4,1999 and Paper 16, filed March 5, 1999.

2. Claims 1-4, 6-9, 13, 14, 15, and 18-68 are pending. Examiner acknowledges the cancellation of claims 5, 10, 11, 12, 16 and 17 and addition of new claims 60-68 in Paper 13. Claims 21-59 and 68 remain withdrawn from consideration. Examiner acknowledges a species election in Paper 16 of a soluble fusion protein comprising V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein.

Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 are drawn to the elected species. Claims 3, 9, 13, 15, 60, 62 , 63, 64 and 66 are drawn to non-elected invention and are withdrawn from consideration. Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 are under examination as they read upon the elected species of TCR-bacteriophage coat protein fusion protein IE fusion protein comprising in sequence a V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein.

3. **New rejections under 35 USC 112 first paragraph necessitated by amendment.**

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The soluble TCR wherein the TCR comprises a human Cβ chain fragment claimed in Claim 20 has no clear support in the specification and the claims as originally filed. The specification and claims as originally filed disclose that the TCR fusion protein may be humanized, contain human TCR sequences, but does not specify that the human TCR sequences are derived from the constant domain of the beta chain. The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis by point to page and line number as to why the claimed subject matter has clear support in the specification.

4. Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A.(withdrawn) In claims 1, 2, 4, 6-8, 14, 18, 61, 65, 67, it is unclear what the term "soluble" means. Is the term limited to solubility in aqueous medium? Is the claim language limited to a TCR molecule without any amino acid residues of transmembrane and cytoplasmic regions? Does the term encompass TCR molecules in which amino acids encoding the native transmembrane and cytoplasmic regions are replaced by other residues, IE immunoglobulin constant region genes, etc?
--Applicant's response on page 5 of Paper 13 has been considered and is persuasive. Examiner has interpreted Applicant's response to mean that the fusion protein is soluble under physiological conditions. Examiner has interpreted Applicant's response to mean that the claim language does not encompass sequences from other non-TCR proteins, IE immunoglobulin constant region genes. Any differences should now be pointed out.

B.(withdrawn) The rejection of claims 6, 11, 12, 16, 17, and 19 as indefinite in the recitation of "protein tag" is withdrawn in view of Applicant's persuasive argument.

C.(withdrawn) In claims 1-20, it is unclear what the term "single-chain T cell receptor" means. Must the single chain T cell receptor bind form an antigen binding groove and bind the same antigen as the native TCR from which it was derived?
-- The rejection is withdrawn in view of the amendment to the claims.

D. (withdrawn) The rejections of claim 5, 10-12, 16 and 17 set forth in paragraphs 3D-I of Paper 10 is withdrawn in view of the amendment to the claims.

E. (withdrawn)The rejection of claims 9 and 12 set forth in paragraph 3 K is withdrawn in view of the amendment to the claims.

F. (withdrawn) The rejection of claim 20, as indefinite in the recitation of the term "humanized" is withdrawn in view of the amendment to claim 20 to indicate that the human sequences of the claims is a human TCR beta chain constant fragment?

G. (maintained) Claim 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65 and 67 recites TCR Vα and Vβ chains. TCR beta chain comprises V regions and C regions (see Choi et al, US Patent 5,616,472, column 2, lines 15-43, in particular). It is unclear what amino acid residues are encompassed by the claim language. Does the V chain include VDJ regions of beta chains and VJ of alpha chains ? Applicant is required to point out the metes and bounds of the term. It is suggested that the

claims be amended to refer "V regions" and "C regions" and not "V chains" and "C regions" and point out which amino acid residues of TCR are encompassed by the claim language.
- Applicant's response on pages 7-8 has been considered but is not persuasive. Applicant's referral to the specification on page 2 does not help to identify which regions are included in the "V chain" claimed in the claims. Similarly Applicant's reference to Choi US 5, 616,472 does not help to identify which regions of the alpha or beta chain are encompassed by the claim language. Applicant is urged to amend the claims to refer to "V regions" and "C regions" and point out which amino acid residues of TCR are encompassed by the claim language. It is unclear if the "V chain" must encompass VDJ regions of the beta chain or if the claim language encompasses TCR fragments of the variable region of alpha or beta chain, IE a fusion protein comprising Vα- VJ region of beta chain- constant region of beta chain. Clarification is required.

H. (NEW, necessitated by amendment) In claim 65, it is unclear how the fusion protein claiming a soluble fusion comprising covalently linked in sequence (emphasis added by Examiner) Vα chain -peptide linker-Vβ-Cβ chain fragment-VIII protein-bacteriophage gene III can have a protein tag covalently linked to the C-terminus of the Cβ chain. The claim would read more clearly if it claimed the fusion protein by reciting the components as they are linked in sequence, IE a soluble fusion protein comprising covalently linked in sequence Vα chain -peptide linker-Vβ-Cβ chain fragment-protein tag- VIII protein-bacteriophage gene III, wherein said protein tag is linked to the N-terminus of the bacteriophage gene VIII protein.

5. Claims 1, 2, 4, 6-8, 14, 18, 19, 20, 61, 65, 67 are rejected under 35 U.S.C. 112 first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Reasons are set forth below.

The claims are drawn to a soluble fusion protein comprising a Vα chain -peptide linker-Vβ - bacteriophage protein in which the fusion protein comprises an antigen binding pocket. The claims are enabled only for fusion proteins which comprise a Cβ region. TCR fusion proteins which do not comprise the Cβ region would not expected to comprise an antigen binding pocket since WO 96/18105 further teach that TCR fusion proteins which do not contain the Cβ do not fold into the native conformation (see page 30, line through page 31, line 31, in particular).

6. The rejection of claims under 35 USC 103(a) as unpatentable over Barbas US Patent 5,759,817, Onda et al., Schodin et al., Novotny et al., W0 96/18105, Ward, Kappler et al

(PNAS 91:6462, 1991) and Choi et al. US Patent 5,616,472 (issued April 1, 1997, priority to Aug. 9, 1990) set forth in Paper 10 mailed June 23, 1998 is hereby withdrawn in view of the species election required by the Examiner. The following rejection under 103(a) is a revision of the rejection set forth in Paper 10 and more particularly address the limitations of the elected species of TCR-bacteriophage coat protein fusion protein.

7. Claims 1, 2, 4, 6-8, 14, 18, 19, 20 61, 65, 67 are rejected under 35 U.S.C. 103(a) as unpatentable over WO 96/18105 (issued 13 June 1996) in view of Barbas US 5,759,817 (filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992

Claims 1, 2, 4, 7-8, 14, 18, 19, 20, 61 and 67 are drawn to a soluble fusion protein comprising in sequence V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein. Claims 6 and 65 are drawn said fusion protein further comprising a protein tag. In claim 65 the protein tag is covalently linked to the C-terminus of the Cβ fragment and the N-terminus of the VIII protein.

WO 96/18105 teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). WO 96/18105 further teaches one embodiment of the single chain TCR in which C-terminus of Vα domain is linked to N-terminus of Vβ chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the Vβ chain is linked to the beta chain constant domain (see pages 3 and 5 and Figure 1, in particular). In one embodiment the C terminus of Vβ chain is linked to a alkaline phosphatase (PI) protein tag (see Figure 1, in particular). WO 96/18105 also teaches that the order of the domains within the single chain TCR is interchangeable (see page 5, in particular). WO 96/18105 also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. WO 96/18105 also teach that a preferred embodiments of linkers are composed of amino acids which tend to increase solubility in aqueous solution (see page 8, lines 1-25, in particular). WO 96/18105 further teach that the TCR fusion protein comprising V-α-peptide linker-Vβ-Cβ fusion protein can be linked to additional segments which do not interfere with the essential properties of the encoded molecule (see page 8, lines 5-8, and page 9, lines 1-9, in particular). WO 06/18105 disclose that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an antigen binding pocket. WP 96/18105 exemplifies a TCR fusion protein comprising V-α-peptide linker-Vβ-Cβ-linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see page 17, lines 13-31, in particular). WO 96/18105 further disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase

C (PI-PLC) (see page 17, lines 23-24, in particular). WO 96/18105 also teaches expression of V-α-peptide linker-Vβ-Cβ TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag (see pages 26-30, in particular). WO 96/18105 further teach that such a protein was predominantly accumulated in the inclusion bodies but that the TCR fusion protein could be isolated in one-step nickel affinity chromatograph with a yield of 5-10 mg of TCR fusion protein per liter of bacteria culture. WO 96/18105 further teach that TCR fusion proteins which do not contain the Cβ do not fold into the native conformation (see page 30, line through page 31, line 31, in particular).

The W0 96/18105 further teaches that the single chain TCR may be derivatized by conjugation of group which does not alter the binding characteristics of the single chain TCR (see page 9, lines 2-20, in particular).

Thus WO 96/18105 teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ-protein tag. WO 96/18105 does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein.

However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains.

Onda et al .disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular).

Huse et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα-peptide linker-Vβ-Cβ-protein tag component taught by WO 96/18105 linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Cα and Cβ region was derived from human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

--Applicant's response on pages 8-14 of Paper 16 has been considered in so far as it addresses the revised rejection. Applicant's response that one with skill in the art would not have expected that a single chain TCR-fusion protein be soluble or have native conformation to form an antigen binding pocket are not persuasive. The cited prior art teaches that the TCR fusion proteins comprising Vα-peptide linker-Vβ-Cβ- linked to other residues fold into the native conformation and can be isolated ~~form~~ from cells expressing the fusion proteins. Applicant's argument that one with skill in the art would not have expected to be able to make a large fusion protein such as the claimed TCR-VIII , however, the Fab-VIII taught by Huse et al. is comparable in size to the claimed TCR-VIII protein and Huse et al. teach that vectors and cells expressing VIII fusion proteins can be readily used to express and isolate the VIII fusion proteins.

WO 96/ 18105 also teach the fusion proteins comprising Vα-peptide linker-Vβ-Cβ- linked to other residues (IE histidine tag) can be readily isolated from cells expressing the fusion protein and that fusion proteins fold into their native structure.

8. Examiner believes that all pertinent arguments have been addressed.

9 No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet in Art Unit 1644 whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973 The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha T. Lubet

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
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